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EXAMINER	
REDDIG, PETER J	

ART UNIT	PAPER NUMBER
1642	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

PTO-PAT-Email@rfem.com

Office Action Summary	Application No.	Applicant(s)	
	10/521,410	ULLRICH ET AL.	
	Examiner	Art Unit	
	PETER J. REDDIG	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *July 9, 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14 and 17-36* is/are pending in the application.

4a) Of the above claim(s) *1-9,11,13 and 20-34* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *10,12,14,17-19,35 and 36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/2/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The Amendment filed July 9, 2009 in response to the Office Action of January 26, 2009 is acknowledged and has been entered. Claim 19 has been amended and new claim 36 has been added. Claims 1-9, 11, 13 and 20-34 were previously withdrawn. Claims 10, 12, 14, 17-19, 35 and 36 are currently being examined as drawn to the originally elected species of an Axl protein and an antibody directed against the Axl protein.

Declaration

2. The Declaration of Dr. Thore Hettmann under 37 CFR 1.132 filed July 9, 2009 is insufficient to overcome the rejection of claims 10, 12, 14, 17-19, 35 and 36 based upon their rejection under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement as set forth in the last Office action because: The specific experiments of the declaration do not provide enabling support for the broadly claimed method, see below..

Rejections Maintained

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 10, 12, 14, 17-19 and 35 remain rejected and claim 36 is rejected essentially for the reasons set under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement essentially for the reasons set forth in the Office Action of January 26, 2009, section 5-pages 2-6, which is based on the rejection set forth in the Office Action of October 19, 2007, sections 7 and 8, pages 4-16.

Examiner argued in the Office Action of October 19, 2007:

Claims 10, 12, and 14-19 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The claims are drawn to a method of reducing the invasivity of malignant disorders comprising inhibiting the AXL protein function with an antibody directed against the Axl protein.

The specification teaches that overexpression of the receptor tyrosine kinase AXL/UFO (Genbank accession No. M 76125) has been implicated in the development of human hematological malignancies. Further, very recent data indicate that signaling of AXL and its ligand GAS6 is involved in angiogenesis, adhesion and survival of cancer cells, see p.1, lines 15-19.

The specification teaches that Axl mRNA was expressed in primary breast cancer tumors, and other tumors and cancer cell lines (kidney, prostate and glioblastomas) as well, see p. 25, line 22 to p. 26, line 10 and Fig. 2-4.

The specification teaches that an antibody to the extracellular domain of Axl can inhibit the invasion of breast cancer cell lines and a prostate cancer cell line into Matrigel in a Boyden chamber *in vitro* assay, see p. 26, lines 24-28 and figure 6.

The specification teaches that the present invention relates to the diagnosis or the prevention and/or treatment of malignant disorders, particularly the tumor invasivity and/or metastasis formation in malignant disorders. Preferred examples of malignant disorders are cancers of the breast, prostate, kidney, colon, lung and glioblastomas. More preferably, the malignant disorder-is breast cancer or glioblastomas, see p. 5, lines 14-19.

One cannot extrapolate the teachings of the specification to the enablement of the claims because no nexus has been established between inhibiting Axl protein function with an antibody directed against said protein and reducing the invasivity of malignant disorders and because 1) the artifactual nature of cell culture systems is well known in the art 2) mRNA does not predictably correlate with protein expression and neither the specification nor the art of record teaches the Axl protein is overexpressed in malignant disorders and 3) the development of therapeutics for malignant disorders such as cancer is well known in the art to be unpredictable

1) As drawn to the artifactual nature of cell culture systems in particular, it is well known in the art that the characteristics of cultured cell lines generally differ significantly from the characteristics of the primary tumor. As discussed in Freshney (Culture of Animal Cells, A Manual of Basic Technique, Alan R. Liss, Inc., 1983, New York, p. 4), it is recognized in the art that there are many differences between cultured cells and their counterparts *in vivo*. These

differences stem from the dissociation of cells from a three-dimensional geometry and their propagation on a two-dimensional substrate. Specific cell interactions characteristic of histology of the tissue are lost. The culture environment lacks the input of the nervous and endocrine systems involved in homeostatic regulation in vivo. Without this control, cellular metabolism may be more constant *in vitro* but may not be truly representative of the tissue from which the cells were derived. This has often led to tissue culture being regarded in a rather skeptical light (p. 4, see Major Differences *In Vitro*). Further, Dermer (Bio/Technology, 1994, 12:320) teaches that, a petri dish cancer is a poor representation of malignancy, with characteristics profoundly different from the human disease. Dermer further teaches that when a normal or malignant cell adapts to immortal life in culture, it takes an evolutionary-type step that enables the new line to thrive in its artificial environment and thus transforms a cell from one that is stable and differentiated to one that is not. The reference states that evidence of the contradictions between life on the bottom of a lab dish and in the body has been in the scientific literature for more than 30 years. Clearly it is well known in the art that cells in culture exhibit characteristics different from those *in vivo* and cannot duplicate the complex conditions of the *in vivo* environment involved in host-tumor and cell-cell interactions. Further, the art recognizes the problem of molecular artifacts associated with cell culture. For example, Drexler et al (Leukemia and Lymphoma, 1993, 9:1-25) specifically teach, in the study of Hodgkin and Reed-Sternberg cancer cells in culture, that the acquisition or loss of certain properties during adaptation to culture systems cannot be excluded. This is exemplified by the teachings of Zellner et al (Clin. Can. Res., 1998, 4:1797-1782) who specifically teach that products are overexpressed in glioblastoma (GBM)-derived cell lines which are not overexpressed *in vivo*. Drexler et al further teach that only a few cell lines containing cells that resemble the *in-vivo* cancer cells have been established and even for the *bona fide* cancer cell lines it is difficult to prove that the immortalized cells originated from a specific cancer cell (see attached abstract). More recently, Zips et al (In vivo, 2005, 19:1-7) specifically teaches that despite their importance for drug testing, *in vitro* methods are beset by pitfalls and inherent limitations (p. 3, col. 1). In particular the authors state that "It is obvious that cells in culture represent an artificial and simplified system. Unlike the situation *in vitro,* a tumor is a 3-dimensional complex consisting of interacting malignant and non-malignant cells. Vascularisation, perfusion and thereby, drug access to the tumor cells are not evenly distributed and in this fact consists an important source of heterogeneity in tumor response to drugs that does not exist *in vitro*. Therefore, prediction of drug effects in cancer patients based solely on *in vitro* data is not reliable and further evaluations in animal tumor systems is essential" (p. 3, col. 2). Additionally Clark et al. (US Pat. App. Pub. 20060019256, January 2006) teach that "[a]lthough cell lines have led to remarkable advances in our understanding of the molecular and biochemical changes in cancer cells, their use in the identification of effective cancer therapies is somewhat limited. Cell lines are imperfect predictors of drug efficacy in de novo tumors. Several factors likely account for this deficiency. Cancer cell lines are selected from a sub-population of cancer cells that are specifically adapted to growth in tissue culture and the biological and functional properties of these cell lines can change dramatically. Furthermore, cancer cells from only a minority of breast cancer tumors establish cell lines or xenograft tumors. The phenotypic and functional characteristics of these cell lines can change drastically relative to their properties in vivo. For example, the marker expression of both normal hematopoietic and leukemic tissue culture cells can change rapidly in tissue culture and often does not reflect that of

the original stem cells from which they were derived. Even when conditions are devised to permit the proliferation of normal stem cells in culture, the conditions often promote self-renewal or differentiation in a way that prevents the stem cells in culture from recapitulating the hierarchy of cell populations that exist in vivo. Taken together, these observations suggest that the biological properties of cell lines can differ markedly from the cancer cells from which they were derived. This likely explains at least in part why the cell lines often are poor predictors of a drug's efficacy in the clinic," see para. 0109.

Thus, based on the cell culture data presented in the specification, in the absence of data demonstrating that antibody directed against the Axl protein can reduce invasivity of malignant disorders in an appropriate *in vivo* model system, no one of skill in the art would believe it more likely than not that the invention would function as claimed, that is reducing the invasivity of malignant disorders, based only on the cell culture data provided.

2) As drawn to the predictability of correlating mRNA and protein expression, Greenbaum *et al.* (Genome Biology, 2003, Vol. 4, Issue 9, pages 117.1-117.8) cautions against assuming that mRNA levels are generally correlative of protein levels. The reference teaches (page 117.3, col. 2) that primarily because of a limited ability to measure protein abundances, researchers have tried to find correlations between mRNA and the limited protein expression data, in the hope that they could determine protein abundance levels from the more copious and technically easier mRNA experiments. To date, however, there have been only a handful of efforts to find correlations between mRNA and protein expression levels, most notably in human cancers and yeast cells. These studies, for the most part, have reported only minimal and/or limited correlations. The reference further teaches (page 117.4, col. 2) that there are presumably at least three reasons for the poor correlations generally reported in the literature between the level of mRNA and the level of protein, and these may not be mutually exclusive. First, there are many complicated and varied post-transcriptional mechanisms involved in turning mRNA into protein that are not yet sufficiently well defined to be able to compute protein concentrations from mRNA; second, proteins may differ substantially in their *in vivo* half lives; and/or third, there is a significant amount of error and noise in both protein and mRNA experiments that limit our ability to get a clear picture. The reference further notes (page 117.6, page col. 2) that to be fully able to understand the relationship between mRNA and protein abundances, the dynamic processes involved in protein synthesis and degradation have to be better understood.

Additional evidence abounds in which protein levels do not correlate with steady state mRNA levels or alterations in mRNA levels in both cancer and normal cell types. For instance, Hell et al. (Laboratory Investigation, 1995, 73: 492-496) teach that cells in all types of Hodgkin's disease exhibited high levels of Bcl-2 mRNA, while the expression of the Bcl-2 protein was not homogenous to said cells. In addition, Fu et al. (EMBO J., 1996, 15:43982-4401) teach that levels of p53 protein expression do not correlate with levels of p53 mRNA levels in blast cells taken from patients with acute myelogenous leukemia, said patients being without mutation in the p53 gene. Vallejo et al. (Biochimie, 2000 82:1129-1133) teach that no correlation was found between NRF-2 mRNA and protein levels suggesting post-transcriptional regulation of NRF-2 protein levels. These references serve to demonstrate that levels of RNAs cannot be relied upon to anticipate levels of protein. Further, Jang et al. (Clinical Exp. Metastasis, 1997, 15: 469-483) teach that further studies are necessary to determine if changes in protein levels track with changes in mRNA levels for metastasis associated genes in murine tumor cells, thus providing

further evidence that one of skill in the art cannot anticipate that the level of a specific mRNA expressed by a cell will be paralleled at the protein level due to complex homeostatic factors controlling translation and post-translational modification. Thus, in the absence of objective evidence demonstrating that not only the Axl mRNA, but also the Axl protein, is differentially expressed in malignant disorders *in vivo*, one would not be able to predictably use the claimed invention for the contemplated method of reducing the invasivity of malignant disorders comprising inhibiting Axl protein function with antibody to Axl based only on the measurement of Axl mRNA levels to determine the expression of the Axl protein as taught in the specification as originally filed.

3) As drawn to the unpredictability of drug development for malignant disorders such as cancer, it is well known that the art of anticancer drug discovery for cancer therapy is highly unpredictable, for example, Gura (Science, 1997, 278:1041-1042) teaches that researchers face the problem of sifting through potential anticancer agents to find ones promising enough to make human clinical trials worthwhile and teach that since formal screening began in 1955, many thousands of drugs have shown activity in either cell or animal models but that only 39 have actually been shown to be useful for chemotherapy (p. 1041, see first and second para). Furthermore, Kaiser (Science, 2006, 313, 1370) teaches that 90% of tumor drugs fail in patients, see 3rd col., 2nd to last para. Additionally, Young et al. (US Patent Application Pub. 20040180002, September 15, 2004) teach that there have been many clinical trials of monoclonal antibodies for solid tumors. In the 1980s there were at least 4 clinical trials for human breast cancer which produced only 1 responder from at least 47 patients using antibodies against specific antigens or based on tissue selectivity. Young et al. teach that It was not until 1998 that there was a successful clinical trial using a humanized anti-her 2 antibody in combination with cisplatin (para 0010 of the published application). The same was true in clinical trials investigating colorectal cancer with antibodies against glycoprotein and glycolipid targets, wherein the specification specifically teaches "to date there has not been an antibody that has been effective for colorectal cancer. Likewise there have been equally poor results for lung, brain, ovarian, pancreatic, prostate and stomach cancers" (para 0011 of the published application). Thus, it is clear that the art recognizes that it could not be predicted, nor would it be expected that based only on the *in vitro* data presented in the specification that it would be more likely than not that the claimed method could be effectively used for the reducing the invasivity of malignant disorders.

Further, the refractory nature of cancer to drugs is well known in the art. Jain (Sci. Am., 1994, 271:58-65) teaches that tumors resist penetration by drugs (p.58, col. 1) and that scientists need to put expanded effort into uncovering the reasons why therapeutic agents that show encouraging promise in the laboratory often turn out to be ineffective in the treatment of common solid tumors (p. 65, col. 3). Curti (Crit. Rev. in Oncology/Hematology, 1993, 14:29-39) teaches that solid tumors resist destruction by chemotherapy agents and that although strategies to overcome defense mechanisms of neoplastic cells have been developed and tested in a number of patients, success has been limited and further teaches that it is certainly possible that cancer cells possess many as yet undefined additional molecular mechanisms to defeat chemotherapy treatment strategies and if this is true, designing effective chemotherapeutic regimens for solid tumors may prove a daunting task (para bridging pages 29-30) and concludes that knowledge about the physical barriers to drug delivery in tumors is a work in progress (p. 36, col. 2). It is

clear that based on the state of the art, in the absence of *in vivo* experimental evidence, no one skilled in the art would accept the assertion that an antibody directed against the AXL protein could predictably be used in a method of reducing the invasivity of malignant disorders. Again, no evidence has been presented that in the *in vivo* environment, the antigen to which the claimed antibody binds is differentially expressed on cancer as compared with normal cells. In addition, anti-tumor antibodies must accomplish several tasks to be effective. They must be delivered into the circulation that supplies the cancer and interact at the proper site of action and must do so at a sufficient concentration and for a sufficient period of time. Also, the target cell must not have an alternate means of survival despite action at the proper site for the antibody. In addition variables such as biological stability, half-life or clearance from the blood are important parameters in achieving successful therapy. The antibody may be inactivated *in vivo* before producing a sufficient effect, for example, by degradation, immunological activation or due to an inherently short half-life of the antibody. In addition, the antibody may not otherwise reach the target because of its inability to penetrate tissues or cells where its activity is to be exerted, may be absorbed by fluids, cells and tissues where it has no effect, circulation into the target area may be insufficient to carry the antibody and a large enough local concentration may not be established.

Given the above, in the absence of *in vivo* experimental data demonstrating reduction of invasivity of malignant disorders with an antibody against AXL, one of skill in the art could not predictably practice the claimed invention without undue experimentation.

Applicant is reminded that MPEP 2164.03 teaches "the amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the stare of the art as well as the predictability of the art. In re Fisher, 428 F.2d 833, 166 USPQ 18, 24 (CCPA 1970) the amount of guidance or direction refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly state in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as how to make and use the invention in order for it to be enabling. Given only lack of guidance in the specification, no one skilled in the art would accept the assertion that the claimed invention would function as contemplated or as claimed based only on the information in the specification and that known in the art at the time the invention was made.

The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict that the invention will function as contemplated or claimed with a reasonable expectation of success. For the above reasons, it appear that undue experimentation would be required to practice the claimed invention.

If Applicants were able to overcome the rejections set forth above under 35 U.S.C. 112, claims 10, 12, and 14-19 would still be rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of reducing the invasivity of **breast and prostate cancer** comprising inhibiting the AXL gene expression and/or AXL ligand gene expression and/or protein function and/or protein ligand function, does not reasonably provide enablement for a method of reducing the invasivity of **malignant disorders** comprising inhibiting the AXL gene expression and/or AXL ligand gene expression and/or protein function

and/or protein ligand function. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The claims are drawn to a method of reducing the invasivity of malignant disorders comprising inhibiting the AXL protein function with an antibody directed against the Axl protein.

This means that the claimed method can be used to reduce the invasivity of any malignant disorder.

The specification teaches as set forth above.

One cannot extrapolate the teachings of the specification to the scope of the claims because the heterogeneity of cancer phenotypes is well known in the art.

In particular, cancers comprise a broad group of malignant neoplasms divided into two categories, carcinoma and sarcoma. The carcinomas originate in epithelial tissues while sarcomas develop from connective tissues, see Taber's Cyclopedic Medical Dictionary (1985, F.A. Davis Company, Philadelphia, p. 274). Given that not all cancers originate from the same tissue types, it is expected and known that cancers originate from different tissue types have different structures as well as etiologies and would present differently. Thus, it would not be predictably expected that a nexus, for example drawn to a connection between AXL, breast and prostate cancer, and cancer invasivity, would be established between cancer types that arose from different tissue types. Further, it is well known that even two carcinomas that present on the same organ have significant differences in etiology and genetic constitution. For example, Busken, C et al, (Digestive Disease Week Abstracts and Itinerary Planner, 2003, abstract No: 850), teach that there is a difference in COX-2 expression with respect to intensity, homogeneity, localization and prognostic significance between adenocarcinoma of the cardia and distal esophagus, suggesting that these two cancers have different etiology and genetic constitution (last five lines of the abstract). Additionally, Kaiser (Science, 2006, 313, 1370) teaches that in a genomic analysis of mutations in breast and colon cancers, it was found that the cancer genes differ between each colon and breast cancers and each tumor had a different pattern of mutations. Kaiser teaches that the steps to cancer may be more complex than had been anticipated, see 3rd col. Furthermore Krontiris and Capizzi (Internal Medicine, 4th Edition, Editor-in-chief Jay Stein, Elsevier Science, 1994 Chapters 71-72, pages 699-729) teach that the various types of cancers have different causative agents, involve different cellular mechanisms, and, consequently, differ in treatment protocols. Chemotherapeutic agents are frequently useful against a specific type of neoplasm and especially with the unpredictability of the art there are no drugs broadly effective against all forms of cancer, see Carter, S. K. et a1. Chemotherapy of Cancer; Second edition;

John Wiley & Sons: New York, 1981; appendix C. Given the above, it is clear that it is not possible to predictably extrapolate a correlation between AXL, and cancer invasivity in any tumor type other than breast and prostate cancer, based on the information in the specification and known in the art without undue experimentation.

Applicant is reminded that MPEP 2164.03 teaches "the amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability of the art. In re Fisher, 428 F.2d 833, 166 USPQ 18, 24 (CCPA 1970) the amount of guidance or direction refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly state in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as how to make and use the invention in order for it to be enabling. Given only lack of guidance in the specification, no one skilled in the art would accept the assertion that the claimed invention would function as contemplated or as claimed based only on the information in the specification and that known in the art at the time the invention was made.

The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict that the invention will function as contemplated or claimed with a reasonable expectation of success. For the above reasons, it appears that undue experimentation would be required to practice the claimed invention.

Applicants argue that The Examiner asserts that Voskoglou-Nomikos does not teach that studies of cell lines are predictive for methods of reducing invasivity of cancer cells and indicates that panels of cell lines are required to provide predictive information and that the data may not be applicable to non-cytotoxic drugs (see paragraph bridging pages 4235-4236). Further, the Examiner asserts that although Khleif teaches that animal models are generally acceptable in drug development, no evidence has been presented that demonstrates that an antibody or other agent against AXL can reduce the invasivity of cancer cells *in vivo*. The Examiner contends that the presented in vivo data does not show a purely *in vivo* effect because tumor cells were altered *in vitro* (truncation of UFO/AXL) prior to implantation.

Applicants argue that submitted herewith is a declaration signed by Dr. Thore Hettmann presenting experimental data which shows the effects of rat anti-AXL antibodies on human prostate carcinoma growth in nude mice. Specifically, PC-3-LN prostate carcinoma cells were implanted into the prostate of NMRI-nu/nu mice. Compared with a control antibody, the rat anti-AXL antibody reduced overall growth of PC-3-LN prostate tumors in nude mice (see Figure 1 of the declaration)

Applicants argue that further, the data presented herewith shows that the anti-AXL antibody reduced the occurrences of spleen metastases compared with control, as well as the known cancer drug Sutent® (see Figure 2 of the declaration).

Applicants argue that thus, Dr. Hettmann concludes that the presented data has demonstrated effective reduction in the invasiveness of non-altered tumor cells implanted in mice by administering an AXL inhibitor in vivo.

Applicants argue that the above data demonstrations the effective reduction of invasivity of unaltered tumor cells implanted in an animal by administering an AXL inhibitor or antibody as requested by the Examiner. Therefore, Applicants believe that claims 10, 12, 14, 17-19, and 35 do provide enabling disclosure.

Applicants' arguments have been considered, but have not been found persuasive. Although declaration of Dr. Thore Hettmann demonstrates that an antagonist anti-AXL antibody reduced the occurrences of spleen metastases compared with control, the claims are not so limited. The claims encompass reducing the invasivity of breast, prostate, kidney cancer cells and cancer cells of epithelial origin with an inhibitor of the AXL protein. Thus, although the specification teaches that antibodies to AXL reduces the invasive activity breast and prostate

cancer cells (see p. 26 and Fig. 6) and the declaration demonstrates activity of an anti-AXL antibody prostate cancer metastases and invasion *in vivo*, given the unpredictability of developing new cancer therapeutics and the unpredictable and heterogeneous response of different cancers to different types of therapeutics previously set forth and in the absence of further guidance or exemplification of additional AXL protein inhibitors on reducing the invasivity of the broadly claimed cancers, one of skill in the art would not be able to predictably use the method as claimed for the reasons previously set forth and above except in breast and prostate cancer with inhibitory anti-AXL antibodies or Fab, Fab', Fab2 or scFV antigen binding fragments thereof. Furthermore, it is noted that the antibody fragments of new claim 36 are not specifically limited to antibody fragments that bind to the Axl protein. One of skill in the art would not predictably expect that antibody fragments that do not bind to Axl would be effective for inhibiting the activity of the Axl protein and reducing the invasivity of cancer cells.

4. Claims 10, 12, 14, 17, 18 and 35 remain rejected as failing to comply with the written description requirement Office Action of January 26, 2009, section 9-pages 7-9.

The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are broadly drawn to a method of reducing invasivity of cancer cells . . . comprising administering an inhibitor of the AXL protein. The claims lack any limitation on said inhibitor of the AXL protein and thus are drawn to a genus of inhibitors of the AXL protein. When given the broadest reasonable interpretation, the term "inhibitor of the AXL protein" encompasses any "inhibitor of the AXL protein" such as a protein, peptide, antibody, low molecular weight, thus the genus of compounds is highly variant which vary significantly both in structure and function from each other. The description of a polyclonal antibody directed to the extracellular portion of AXL that inhibits the migration of cell lines *in vitro* (see p. 26-lines 24-28 and Fig. 6) fails to adequately describe the genus of agents because said genus tolerates members which differ significantly in both structure and function from said antibody to AXL protein One of skill in the art can reasonably conclude that applicant was not in possession of a genus of term "inhibitor of the AXL protein at the time the invention was filed. Because the

genus of term "inhibitor of the AXL protein" is not adequately described, the method claims relaying on said genus are also not adequately described.

Although drawn to DNA arts, the findings in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997) and Enzo Biochem, Inc. V. Gen-Probe Inc. are relevant to the instant claims. The Federal Circuit addressed the application of the written description requirement to DNA-related inventions in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). The court stated that "[a] written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." Id. At 1567, 43 USPQ2d at 1405. The court also stated that a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA" without more, is not an adequate written description of the genus because it does not distinguish the genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is. Id. At 1568, 43 USPQ2d at 1406. The court concluded that "naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material." Id.

It is noted that as of the filing date antibodies that inhibit AXL protein activity were known in the art (see U.S. Pat. No. 5,468,634 col. 7, line 60 to col. 8 line 30, previously cited), however, these antibodies fail to adequately describe an entire genus because the genus is highly variant encompassing members which differ significantly in structure from the few art known antibody inhibitors.

In the instant case the genus is only described as a definition by function (i.e. inhibition of AXL protein), and beyond the examples of antibodies, one of skill in the art cannot readily visualize or recognize the identity of members of the genus.

Applicants argue that Claims 10, 12, 14, 17, 18, and 35 have been rejected under 35 U.S.C. 112, second paragraph, as failing to comply with the written description requirement. The Examiner asserts that the specification does not define any structural features commonly possessed by members of the genus "inhibitor of the AXL protein". Applicants submit that there is written support for inhibitors of the AXL protein on page 6, line 16 to page 8, line 4 of the specification. Those skilled in the art at the time of filing would know how to produce antibodies, proteolytic fragments, e.g. Fab, Fab', or Fab2 fragments, scFV fragments,

biologically active nucleic acids, peptides, low molecular weight AXL kinase inhibitors, AXL analogues, etc. based on the DNA sequence of the AXL gene and the protein sequence of AXL which were publicly available at the time of filing. Therefore, Applicants submit that the specification as filed provides satisfies the written description requirement for a method of reducing the invasivity of cancer cells in a subject in need thereof. Therefore, Applicants respectfully request that the rejection of claims 10, 12, 14, 17, 18, and 35 be withdrawn.

Applicants' arguments have been considered, but have not been found persuasive. Although the specification names potential inhibitors of AXL on page 6, line 16 to page 8, line 4, other than antibodies to AXL, the specification does not provide the structure of these inhibitors or any structure function correlation between the named inhibitors and their functions. As previously set forth, the naming of material generally known to exist is insufficient to describe the material in the absence of knowledge of what the material consists of. Thus, recitation of potential inhibitors the AXL protein in the specification is insufficient to describe the broadly claimed genus of the inhibitors of the AXL protein without a known or described structure or structure function correlation of such inhibitors.

Specification

5. The disclosure remains objected to because of the following informalities as set forth in the Office Action of January 26, 2009, section 7-page 7: There are hyperlinks in the specification at p.17, line 22. Removal of the "http://" will disable the hyperlink and obviate this objection.

Applicants have not responded to this objection or amended the specification, thus the objection is maintained.

6. All other objections and rejections recited in Office Action of January 26, 2009are withdrawn.

7. No claims allowed.

8. This action is a **final rejection** and is intended to close the prosecution of this application. Applicant's reply under 37 CFR 1.113 to this action is limited either to an appeal to the Board of Patent Appeals and Interferences or to an amendment complying with the requirements set forth below.

If applicant should desire to appeal any rejection made by the examiner, a Notice of Appeal must be filed within the period for reply identifying the rejected claim or claims appealed. The Notice of Appeal must be accompanied by the required appeal fee.

If applicant should desire to file an amendment, entry of a proposed amendment after final rejection cannot be made as a matter of right unless it merely cancels claims or complies with a formal requirement made earlier. Amendments touching the merits of the application which otherwise might not be proper may be admitted upon a showing a good and sufficient reasons why they are necessary and why they were not presented earlier.

A reply under 37 CFR 1.113 to a final rejection must include the appeal form, or cancellation of, each rejected claim. The filing of an amendment after final rejection, whether or not it is entered, does not stop the running of the statutory period for reply to the final rejection unless the examiner holds the claims to be in condition for allowance. Accordingly, if a Notice of Appeal has not been filed properly within the period for reply, or any extension of this period obtained under either 37 CFR 1.136(a) or (b), the application will become abandoned.

9. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 C.F.R., 1.136(a).

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R.,

1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Peter J. Reddig whose telephone number is (571) 272-9031. The examiner can normally be reached on M-F 8:30 a.m.-5:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Peter J Reddig/
Examiner, Art Unit 1642